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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Fred R. Kramer

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EXAMINER

PANDE, SUCHIRA

ART UNIT

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1637

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/791,502	Applicant(s) KRAMER ET AL.	
	Examiner SUCHIRA PANDE	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 February 2009 and 07 April 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 17-38 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 17-38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 23, 2009 has been entered.

Claim Status

2. Claims 1-16 are cancelled; claim 37 has been amended. Currently claims 17-38 are active and will be examined in this action.

Response to Arguments

Re 103 rejection of claims 17-23, 25-29, 31-32, and 34-38 over Spiro et al. in view of Tyagi; Bonnet et al. and ; Landers

3. Applicant's arguments, filed February 23, 2009 and also see summary of interview mailed on April 7, 2009, with respect to claims 17-23, 25-29, 31-32, and 34-38 have been fully considered and are persuasive.

Cited art does not teach coding the beads with labeled hairpins that melt under different conditions. Hence the cited 103 rejection of claims 17-23, 25-29, 31-32, and 34-38 over Spiro et al. in view of Tyagi; Bonnet et al. and ; Landers has been withdrawn. Upon further search and consideration Examiner is citing new art that

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suggests use of micro beads with immobilized molecular beacons as target binding site and where coding scheme is based on FRET detection of labeled hairpins.

Re 103 rejection of claims 24 and 30 over Spiro et al.; Tyagi; Bonnet et al. and ; Landers as applied to claims 22 and 17 above further in view of Walt et al.

4. Since 103 rejections of claims 22 and 17 over cited primary art combination has been withdrawn, hence rejections of claims 24 and 30 further in view of secondary art Walt et al. is no longer valid and is accordingly withdrawn.

Re 103 rejection of claim 33 over Spiro et al.; Tyagi; Bonnet et al. and ; Landers as applied to claim 17 above further in view of Frutos et al.

5. Since 103 rejections of claim 17 over cited primary art combination has been withdrawn, hence rejections of claim 33 further in view of secondary art Frutos et al. is no longer valid and is accordingly withdrawn.

Re objection to claim 37

6. Amendment to claim 37 corrects the antecedent basis, thus it obviates the objection cited in previous office action and is acceptable.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

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the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 17-23, 25-29, 31-32, and 34-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi (2000) Nature Biotechnology vol. 18 pp 597-598 (previously cited) and Lee et al. (WO 00/14278 published March 16, 2000—provided by Applicant in IDS) in view of Tyagi et al. (1998) Nature Biotechnology vol. 16 pp 49-53 (provided by Applicant in IDS).

Regarding claims 17, Tyagi (2000) teaches a hybridization assay for at least one of a multiplicity of nucleic acid sequences in an analyte comprising the steps of:

(a) contacting said analyte with a mixture of encoded microcarriers having immobilized on their surfaces (see page 597 Fig. 1 where contacting said analyte with a mixture of microcarrier—microbead is shown)

(i) a hybridization probe for one of said multiplicity of sequences, (see Fig. 1, where capture probe is shown immobilized on microbead thus teaching a hybridization probe for one of said multiplicity of sequences) whose hybridization to said at least one sequence can be detected (see page 598 Figure 2 where detection of hybridized sequences is taught) and

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(b) forming a distributed array of said microcarriers wherein location of said microcarriers in said distributed array is not used to identify said at least one nucleic acid sequence (see page 598 column 2 last par. where formation of a distributed array of said microcarriers is taught. See page 598 column 3 1st par. wherein location of said microcarriers in said distributed array is not used to identify said at least one nucleic acid sequence is taught) ;

(c) determining which microcarriers have hybridization probes hybridized to said at least one nucleic acid sequence of said analyte (see page 598 column 3 1st par. where determination of identity of each microbead and the identity of its cargo as it flies past the detector of fluorescence activated cell sorter is taught. Thus teaching determining which microcarriers have hybridization probes hybridized to said at least one nucleic acid sequence of said analyte); and

(d) optically decoding the microcarriers having said at least one nucleic acid sequence hybridized to its hybridization probes to identify said at least one nucleic acid sequence (see page 598 column 3 1st par. where determination of identity of each microbead and the identity of its cargo as it flies past the detector of fluorescence activated cell sorter (FACS) is taught. By teaching detection using FACS, Tyagi inherently teaches optically decoding the microcarriers having said at least one nucleic acid sequence hybridized to its hybridization probes to identify said at least one nucleic acid sequence)

Regarding claim 21 Tyagi teaches wherein steps (c) and (d) include decoding all microcarriers (see page 598 col. 3 par. 1 where analysis of fluid array by Fluorescence

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activated cell sorter (FACS) to determine optical bar code of each microbead is taught.

Thus teaching wherein steps (c) and (d) include decoding all microcarriers.

Regarding claims 25 and 34 Tyagi teaches wherein steps (c) and (d) include flow cytometry (see above where FACS is taught thus by teaching FACS Tyagi teaches wherein steps (c) and (d) include flow cytometry).

Regarding claims 27-28 and 31 Tyagi teaches method of claim 17 including steps a) and b) as described above. Claims 27 and 31 require that step (a) precede step (b) and claim 28 requires that step (b) precede step (a). Tyagi does teach wherein step (a) precedes step (b). (see page 598 2nd last par where hybridization to encoded microbeads preceeds formation of distributed random array). Base claim 17 has been written using open language comprising. Hence to one of ordinary skill in the art it is obvious as to the order of sequence in which these two steps are conducted. This will depend on the type of assay being conducted. See MPEP 2144.04 IV c. 2144.04 Legal Precedent as Source of Supporting Rationale [R-1]. CHANGES IN SIZE, SHAPE, OR SEQUENCE OF ADDING INGREDIENTS. Changes in Sequence of Adding Ingredients See *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results).

Regarding claims 29 and 35 Tyagi teaches wherein said distributed array is a planar array (see page 598 2nd last par last sentence where assembly of fixed array is taught. By teaching fixed array Tyagi teaches a planar array because microbeads are fixed on to a surface or a plane).

Regarding claim 36 Tyagi teaches wherein said distributed array is a linear array (see page 598 col. 3 par. 1 where detection of identity of each microbead in the fluid array using FACS is taught. Here the FACS determines the optical barcode of each bead as it flies past the detector is taught. Thus by teaching a fluid array where each microbead flies past detector this inherently requires a sequential passage one after another past detector which means the array of beads in this set up is linear, hence Tyagi teaches said distributed array is a linear array).

Regarding claim 17 Tyagi does not teach

(a) (ii) a coding scheme comprising a plurality of signaling hairpins that are not hybridization probes for said multiplicity of sequences, including said at least one sequence, comprising quenched, fluorephore-labeled hairpin molecules each comprising an interacting affinity pair separated by a linking moiety, one member of said affinity pair having bound thereto at least one quenched fluorophore, wherein interaction of the affinity pair is disruptable to unquench said at least one fluorophore by a physical or chemical change in a condition of its environment, wherein the disruption of the interaction of at least one affinity pair occurs at a first level of said condition and the disruption of the interaction of at least another affinity pair occurs at a second level of said condition, and wherein said disruptions are optically differentiable, and wherein the coding scheme for identifying individual microcarriers in said mixture comprises a combination of multiple spectrally differentiable fluorophores and multiple affinity pairs disruptable at detectably different levels of said condition;

(d) optically decoding the microcarriers by changing said condition to said detectably different levels to disrupt quenching, and detecting changes in fluorescence from the signaling hairpins.

Regarding claim 17 Lee and Brightwell teach

(a) (ii) a coding scheme comprising a plurality of signaling hairpins (see page 3 lines 23-25 where temperature probe in form of hairpin is taught. See page 2 lines 6-15 where signalling based on denaturation of fluorescently labeled double stranded temperature probe at predetermined temperature is taught. Thus Lee and Brightwell teach signaling hairpin) that are not hybridization probes for said multiplicity of sequences (see page 5 lines 7-9 where addition of signal sequences to reaction is taught in order to provide the basis for temperature probe. Thus Lee and Brightwell teach these signaling sequences are not hybridization probes for said multiplicity of sequences)

including said at least one sequence, comprising quenched, fluorphore-labeled hairpin molecules each comprising an interacting affinity pair separated by a linking moiety, one member of said affinity pair having bound thereto at least one quenched fluorophore (see fig. 2 where hairpin temperature probe shown meets all the limitations recited above), wherein interaction of the affinity pair is disruptable to unquench said at least one fluorophore by a physical or chemical change in a condition of its environment (see page 4 lines 6-10 where upon denaturation the disruption of affinity pair is taught so FRET no longer occurs thus teaching wherein interaction of the affinity pair is disruptable to unquench said at least one fluorophore by a physical or chemical change

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(by teaching denaturation Lee and Brightwell inherently teach a physical or chemical change that causes denaturation) in a condition of its environment), wherein the disruption of the interaction of at least one affinity pair occurs at a first level of said condition and the disruption of the interaction of at least another affinity pair occurs at a second level of said condition (see page 5 line 11-15 where temperature probes are designed so that it denatures at any desired predetermined temperature--- thus teaching disruption at specific desired temperature. Also see page 5, lines 34-37 where more than one temperature probe may be added is taught. This is done to provide appropriate and preferably different signals when the predetermined extension and /or denaturation temperatures have been reached. Thus Lee and Brightwell teach wherein the disruption of the interaction of at least one affinity pair occurs at a first level of said condition (1st condition = for example extension temperature) and the disruption of the interaction of at least another affinity pair occurs at a second level of said condition (2nd condition = for example denaturation temperature)),

and wherein said disruptions are optically differentiable(see page 5 lines 35-36 where appropriate and preferably different signals are taught when predetermined temperatures are reached. Also see page 4 lines 1-4 where FRET based fluorescence signal measurements are taught. Thus by teaching appropriate and preferably different FRET based signals, Lee and Brightwell teach and wherein said disruptions are optically differentiable), and

(d) optically decoding the microcarriers by changing said condition to said detectably different levels to disrupt quenching, and detecting changes in fluorescence

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from the signaling hairpins (see page 5 lines 26-35 where use of different probes designed to denature at different temperatures is taught. Since FRET based labeling of the signaling hairpins and detection has been taught see above—hence Lee and Brightwell inherently teach optically decoding the microcarriers by changing said condition to said detectably different levels to disrupt quenching, and detecting changes in fluorescence from the signaling hairpins) .

Regarding claim 17, Tyagi (2000) teaches use of coded microbeads but does not teach wherein the coding scheme for identifying individual microcarriers in said mixture comprises a combination of multiple spectrally differentiable fluorophores and multiple affinity pairs disruptable at detectably different levels of said condition.

Regarding claim 17, Lee and Brightwell as described above implicitly teach a combination of multiple spectrally differentiable fluorophores and multiple affinity pairs disruptable at detectably different levels of said condition.

Regarding claim 17, Lee and Brightwell do not explicitly recite a combination of multiple spectrally differentiable fluorophores that are useful for FRET based detection of labeled hairpins that can be used.

Regarding claim 17, Tyagi et al. (1998) teach a combination of multiple spectrally differentiable fluorophores that are useful for FRET based detection of labeled hairpins (see page 51 par. 1 where multiple fluorophore-quencher pairs are taught. The hairpin labeled with the fluorophore-quencher pairs are non fluorescent in the quenched state when they are present close together in the hairpin however they emit characteristic

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fluorescent color when the hairpin opens up and distance between quencher and fluorophore increases).

Regarding claim 37, Tyagi et al. teaches wherein said hybridization probe is a molecular beacon probe (see page 50 fig. 1 where molecular beacon is taught).

Regarding claim 38, Tyagi et al. teaches wherein step (c) includes determining how much of said at least one nucleic acid sequence has hybridized.(see page 49 section real time detection of PCR amplicons par. 1 where quantitative determination over wide range of target concentration is taught. Thus by teaching quantitative determination Tyagi et al. teach wherein step (c) includes determining how much of said at least one nucleic acid sequence has hybridized)

Regarding claim 18, Lee and Brightwell teaches wherein said interacting affinity pair comprises complementary oligonucleotide sequences hybridized to one another (See fig. 1 where interacting affinity pair comprises complementary oligonucleotides).

Regarding claim 19, Lee and Brightwell teaches wherein said mixture of signaling hairpins includes at least three affinity pairs.(see page 5 lines 26-37 where detection of predetermined temperatures (annealing, denaturation and extension) using more than one such temperature probe is taught. Thus by teaching three predetermined temperature detection by using more than one probe, Lee and Brightwell necessarily teach wherein said mixture of signaling hairpins includes at least three affinity pairs)

Regarding claim 20, Lee and Brightwell teaches wherein said mixture of signaling hairpins includes from three to eight affinity pairs (see page 6 Example 1 where 5 affinity pairs having 20%, 40%, 50%, 60% and 80% GC content are taught. Thus by

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teaching 5 different affinity pairs Lee and Brightwell teaches wherein said mixture of affinity pairs includes from three to eight affinity pairs). In the specific example taught by Lee and Brightwell 5 different affinity pairs are composed of two complementary strands. In Fig. 2 Lee and Brightwell teach the signaling hairpin.

It would also have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make said mixture of signaling hairpins includes from three to eight affinity pairs as recited in instant claim.

This is consistent with the Federal Circuit decision in In re Peterson, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003) "We have also held that a prima facie case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties." Thus, an ordinary practitioner would have recognized that the number of signaling hairpins could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the number of signaling hairpin was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. As noted, a skilled artisan is capable of designing 3-8 signaling hairpin affinity pairs that have the same GC content as the affinity pair made by using two complimentary linear

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strands. Thus, an ordinary practitioner would have recognized that the results could be adjusted to maximize the desired results. By using hairpins that have different melting temperature and using spectrally distinguishable fluorophores to label each of the hairpin along with the quencher, one of ordinary skill in the art can see that the number of possible uniquely encoded beads increases from 3^n to 8^n where n is the number of spectrally distinguishable fluorophores based on their emission spectra and 3-8 is the number of signaling hairpins. Hence by using a combination of multiple hairpins that differ in melting temperatures along with use of different fluorescence labels one of ordinary skill in the art is now able to uniquely encode many more micro carrier beads that can be optically decoded. Therefore one of ordinary skill in the art would have a reasonable expectation of success in being able to use these encoded beads in high throughput assays where massive parallel processing of multiple samples can be done using the bead format.

Regarding claim 22, Lee and Brightwell teaches wherein said linking moiety comprises an oligonucleotide sequence (see Fig. 2 where the nucleotide of the loop of the signaling hairpin is shown. Thus implicitly teaching said linking moiety comprises an oligonucleotide sequence).

Regarding claims 23 and 32 Lee and Brightwell teaches wherein the step of decoding includes disrupting the hybridized affinity pairs by increasing temperature (see page 5 lines 35-37 where increasing temperature is taught to disrupt different affinity pairs forming the probes designed to measure annealing, extension and denaturation temperature).

Regarding claim 26, Lee and Brightwell teaches wherein a quencher is attached to the complementary oligonucleotide sequence not bearing the at least one fluorophore.(see Fig. 2 where signaling hairpin taught meets this limitation).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Lee and Brightwell and Tyagi et al. (1998) in the method of Tyagi. The motivation to do so is provided to one of ordinary skill by teachings of Tyagi (2000), Lee & Brightwell ; and Tyagi et al. (1998).

Tyagi (2000) describes the advantages associated with using microbeads based optical detection (see page 598 col. 3 last par) where he states "The advantage of such microbead techniques is their statistical robustness because a large number of microbeads can be contained in small volume, and because a large number of microbeads can be rapidly analyzed by flow cytometry or can be simultaneously analyzed by imaging, a high degree of redundancy can be build into the analyses, making them more reliable. These developments point towards a future in which the direct readout of gene expression profiles will be commonplace."

Thus by explicit teaching of Tyagi (2000) one of ordinary skill in the art knows the advantages associated with using microbeads based optical detection. Also one of ordinary skill realizes that in order to achieve direct readout of gene expression profiles as suggested by Tyagi will require a microbead based optical detection system that allows for real time detection. One of ordinary skill in the art realizes that using linear capture probes immobilized on microbeads is not ideal for real time detection. This is because prior art (see whole article Tyagi et al. 1998) teaches to one of ordinary skill by

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a direct comparison of "hairpin probes" with corresponding "linear probes" that hairpin multicolor molecular beacons are better than linear probes as hybridization probes to be used in situation where real time detection is desirable. Further Tyagi et al. teach quantitative real time detection of amplicons formed during PCR using hairpin molecular beacons. In addition they also teach multiple molecular beacons could be designed to detect multiple targets in the same solution simultaneously by using molecular beacons each emitting light of different color. (see Tyagi et al. 1998 page 49 par. 2-4).

Thus one of ordinary skill in the art is motivated to use molecular beacons taught by Tyagi et al. 1998 labeled with different fluorophore and quencher pairs as capture probes in the microbead system taught by Tyagi (2000) with a reasonable expectation of success in being able to perform quantitative real time detection of multiple targets simultaneously.

So if quantitative real time detection of multiple targets is being performed simultaneously using this microbead based detection system, then one of ordinary skill in the art realizes that a robust, specific and sensitive system is needed that will allow continuous independent monitoring of progression of each of these real time reactions.

Lee and Brightwell teach to one of ordinary skill that multiple signaling hairpins can be designed such that they do not serve as capture probes (i.e. they are not molecular beacon probes that have affinity for target) but can be used to optically monitor progression of real time reaction (by use of signalling hairpins that can be disrupted at different desired conditions (different temperature that cause denaturation of signaling hairpins)).

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Array based systems have capability of processing hundreds to thousands of targets simultaneously. Hence a strategy is required that will allow simultaneous monitoring of 100s to 1000s of targets. The principle taught by Lee and Brightwell to design signaling hairpins that disrupt under specified conditions provides a solution to the above problem. By using signaling hairpins that disrupt under specified conditions one of ordinary skill can increase the number of signaling molecules. This is achieved by designing 3 different signaling hairpins that differentially disrupt at each the three stages (three temperatures-denaturation, annealing and extension) of PCR enunciated above. Now these same three different signaling hairpins can be used in combination with each of the target bound to molecular beacon capture probe. So now the final identity of each of the bead will be a combination of the fluorescence emission from the target hybridized to the molecular beacon capture probe plus the fluorescence emission from the signalling hairpin that is denatured under that specific condition. This fluorescence emission from each such microbead containing capture probe and the desired no of signaling hairpins labeled will keep changing depending on how the reaction is progressing which can be optically monitored.

By using hairpins that have different melting temperature and using spectrally distinguishable fluorphores to label each of the hairpin along with the quencher, one of ordinary skill in the art can see that the number of possible uniquely encoded beads increases from 3^n to 8^n where n is the number of spectrally distinguishable fluorophores based on their emission spectra and the number of signaling hairpins ranges from 3-8. Hence by using a combination of multiple hairpins that differ in melting temperatures

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along with use of different fluorescence labels one of ordinary skill in the art is now able to uniquely encode many more microcarrier beads that can be optically decoded.

Therefore one of ordinary skill in the art would have a reasonable expectation of success in being able to use these encoded beads in high throughput assays where massive parallel processing of multiple samples can be done using the bead format.

10. Claims 24 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi (2000); Lee & Brightwell; in view of Tyagi et al. (1998) as applied to claims 17 and 22 above further in view of Walt et al. (2000) Science vol. 287 pp 451-452 (NPL cited in IDS by applicant).

Regarding claims 24 and 30, Tyagi (2000); Lee & Brightwell; in view of Tyagi et al. (1998) teach method of claims 22 and 17 respectively, but regarding claims 24 and 30 they do not teach wherein forming the distributed array comprises immobilizing individual microcarriers at the ends of fibers in a fiber-optic bundle.

Regarding claims 24 and 30, Walt teaches forming the distributed array comprises immobilizing individual microcarriers at the ends of fibers in a fiber-optic bundle (see page 451 par 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Walt in the method of Tyagi (2000); Lee & Brightwell; in view of Tyagi et al. (1998). The motivation to do so is provided by Walt who states "A relative new comer to the array field is the self assembled bead array. This format is a departure from ----approaches and offers the molecular biologist an entirely new platform on which to study gene expression and

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DNA variation. The bead arrays are assembled on an optical fiber substrate". (see page 451 par. 2). They then go on to describe how the fiber optic arrays are made.

11. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi (2000); Lee & Brightwell; in view of Tyagi et al. (1998) as applied to claim 17 above further in view Frutos et al. (US pat. 6,579,680 B2 issued Jun 17, 2003 previously cited).

Regarding claim 33, Tyagi (2000); Lee & Brightwell; in view of Tyagi et al. (1998) teach method of claim 17, but do not teach wherein step (d) includes disrupting said affinity pairs by adding a denaturant.

Regarding claim 33, Frutos et al. teach use of denaturants such as formamide to disrupt said affinity pairs by adding a denaturant (see col. 3 lines 48-52).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use a denaturant (formamide) in the method Tyagi (2000); Lee & Brightwell; in view of Tyagi et al. (1998) to disrupt said affinity pairs. Lee & Brightwell teaches use of temperature to disrupt said affinity pairs. Frutos et al. states "modification of certain hybridization conditions, such as temperature and use of denaturants such as formamide that are known by those in the art to increase stringency of hybridization." (see col. 3 lines 46-52). So art teaches one of ordinary skill that changing temperature or presence of denaturant can be used to alter hybridization, hence one of ordinary skill can use the method that is desired to achieve the same end result namely disrupt said affinity pairs. SEE MPEP 2144.06 Art Recognized Equivalence for the Same Purpose [R-6]. In order to rely on equivalence as a rationale

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supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Conclusion

12. All claims under consideration 17-38 are rejected over prior art.
13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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